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Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☐ THE PERIOD FOR RESPONSE:

a) ☐ is extended to run _____ or continues to run _____ from the date of the final rejection

b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☒ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 9/8/93 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☐ They raise the issue of new matter. (See Note).

   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ ~~Upon the filing an appeal, the proposed amendment ☐ will be entered ☐ will not be entered and~~ The status of the claims ~~will~~ is as follows:

   Claims allowed: NONE
   Claims objected to: NONE
   Claims rejected: 1-51

   However;

   ☐ Applicant's response has overcome the following rejection(s): _____

4. ☒ The [redacted] request for reconsideration has been considered but does not overcome the rejection because See ATTACHMENT

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficent reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☒ Other See ATTACHMENT

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07/446,235
PTOL-303 (REV. 5-89)

SUPPLEMENT TO ADVISORY ACTION

The applicant argues against the rejections of claims 1 - 2, 4, 8, 12 - 14, 19, and 42 - 50 under 35 USC 102(b) as anticipated by Miller et al. or Stein et al on the basis that 1) both references only disclose oligonucleotides with fully modified internucleotide linkages and 2) that neither reference teaches that the alleged oligonucleotides will form RNAse H sensitive duplexes with cellular RNA. These arguments have been fully considered but are not deemed persuasive.

Even though applicants specific invention as defined in the specification may be only partially modified oligonucleotides, the claims are not limited to such. The claimed oligonucleotides read on oligonucleotides whose internucleotide linkages are each modified in order to confer both exonuclease and endonuclease resistance upon the molecule. Secondly, Stein et al. clearly indicates that phosphorothioate oligonucleotides are not only resistant to nuclease degradation by also form duplexes with RNA that make the RNA even more sensitive to RNAse H digestion than duplexes with oligonucleotides with normal phosphodiester internucleotide linkages.

With regard to the obviousness rejection, Walder et al. clearly documents that the prior art recognized the critical importance of antisense inhibitors being capable of hybridizing to RNA and generating RNAse H sensitive. Furthermore, the art also recognized the importance of the antisense inhibitor being resistant to the many nucleases in the blood and tissue (Inoue et al.). In addition, Inoue teaches the uses of only partially modified internucleotide linkages that are resistant to both exonucleases and endonucleases. Consequently, the screening of oligonucleotides for those possessing each of the above critical aspects of effective antisense oligomers would have been well within the skill of the artisan because he would want antisense oligomer with maximal inhibiting properties. Such partially modified oligonucleotides would also have been obvious to the artisan wanting to combine nuclease resistance with the highest possible melting temperature, i.e. highest affinity between modified oligomer and the RNA in the cell.

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